REMARKS

Status of the claims

Claims 4-6, 8-23, 25-85, 88-176, 193 and 197-211 are pending. All grounds of rejection have been overcome by amendment of the claims or argument.

Rejection based on 35 U.S.C. § 102(b)

Claims 4-6, 8 and 31 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Du et al. (U.S. Patent No. 4,450,272.) In particular, the 5th, 6th, 7th, 9th and 10th compounds of table III, wherein Ar_1 is phenyl, Ar_2 is piperazinyl, A is NH, Z is S and R_3 and R_4 are both hydrogen were cited as being anticipatory in the office action. A review of the cited reference suggests that the compounds relied on for the rejection are from table II, and not table III, and that the definition of Ar_2 should be "pyrazinyl" and not "piperazinyl." Therefore, this response accordingly addresses this rejecion as being based on the compounds in table II, which contain a pyrazinyl ring system. If Applicants are mistaken, clarification from the Examiner is respectfully requested.

As amended, claims 4, 8, and 31 are not anticipated by Du et al. Specifically, Applicants have removed "pyrazinyl" from the definition of Ar_2. Consequently,

McDonnell Boehnen Hulbert & Berghoff
300 S. Wacker Drive
Chicago, IL 60606
(312) 913-0001

Applicants request that the rejection based on 35 U.S.C. § 102 (b) be withdrawn.

Rejection based on 35 U.S.C. §112, first paragraph

Claims 4-6, 8-9, 27, 31-32, and 50 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing new matter. The Examiner has suggested that "heterocycle" be replaced with the phrase "saturated heterocyclic ring." Applicants have adopted the Examiner's suggestion in claims 4, 5, 8, 9, 27, 31, 32, and 50.

Applicants note that claim 6 does not contain the objected to term and consequently request that the rejection of claim 6 based on 35 U.S.C. §112, first paragraph be withdrawn.

Applicants also note that in some instances, the word "heterocycle" was not amended to "saturated heterocyclic ring." See for example claim 4, where, in the definition of R_3 and R_4, the phrase "optionally substituted saturated or partially unsaturated heterocycle of from 5 to 8 atoms, which saturated or partially unsaturated heterocycle" was amended to "optionally substituted saturated heterocyclic ring or partially unsaturated heterocycle of from 5 to 8 atoms, which saturated heterocyclic ring or partially

McDonnell Boehnen Hulbert & Berghoff
300 S. Wacker Drive
Chicago, IL 60606
(312) 913-0001

unsaturated heterocycle..." In situations such as this, the term "heterocycle" was originally in the claim and, therefore, does not seem to present any new matter issues.

Applicants respectfully request that the rejections based on 35 U.S.C. §112, first paragraph be reconsidered and withdrawn.

Rejection based on 35 U.S.C. §112, second paragraph

Claims 4-6, 8-23, 25-85, 88-176, 193, 197-211 stand rejected under 35 USC §112, second paragraph, as being indefinite. Specifically, in claim 4 and elsewhere, the phrase "optionally substituted" is objected to as being indefinite. Applicants note that the objected to phrase is defined on pages 42-43 of the application as originally filed and that using the phrase "optionally substituted" avoids unnecessarily long claims.

Claim 193 also stands rejected because the phrase "the compound or salt is not addictive" is allegedly not clear. Applicants respectfully reiterate the arguments made in the prior response and per the Examiner's request, the Applicants are resending a copy of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (the American Psychiatric Association, 2000)

McDonnell Boehnen Hulbert & Berghoff
300 S. Wacker Drive
Chicago, IL 60606
(312) 913-0001

pages 192-198. Consequently, applicants request that the rejection based on 35 U.S.C. §112, second paragraph be withdrawn.

Information Disclosure Statement

Applicants enclose herewith copies of the references cited in the PTO Form 1449 submitted previously. Applicants further note that the reference citations on the form PTO 1449 included with the supplemental information disclosure statement (IDS) were not initialed. It is unclear as to whether the Examiner has considered those references. Applicants respectfully request that the examiner initial the reference citations on the form 1449 and provide the Applicants a copy of the initialed form 1449.

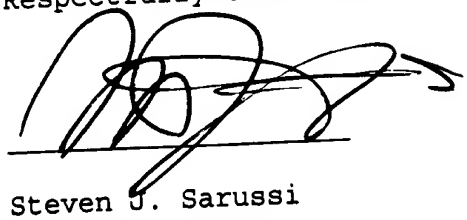
Furthermore, the Applicants are resubmitting all of the references disclosed in the original IDS. These references were not considered because certain unidentified references were apparently missing. Applicants are resending all of the references together with form PTO 1449 and request that they be considered.

McDonnell Boehnen Hulbert & Berghoff
300 S. Wacker Drive
Chicago, IL 60606
(312) 913-0001

Allowance of the elected claims is respectfully solicited. If the Examiner believes that discussion of the application will be helpful, the Examiner is encouraged to contact the undersigned attorney.

Respectfully submitted,

Dated: July 2, 2003

By: 

Steven J. Sarussi
Reg. No. 32,784
McDonnell Boehnen
Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
(312) 913-0001

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

FOURTH EDITION

TEXT REVISION

DSM-IV-TR™

Published by the
American Psychiatric Association
Washington, DC

Copyright © 2000 American Psychiatric Association

DSM, DSM-IV, and DSM-IV-TR are trademarks of the American Psychiatric Association. Use of these terms is prohibited without permission of the American Psychiatric Association.

ALL RIGHTS RESERVED. Unless authorized in writing by the APA, no part of this book may be reproduced or used in a manner inconsistent with the APA's copyright. This prohibition applies to unauthorized uses or reproductions in any form, including electronic applications.

Correspondence regarding copyright permissions should be directed to the DSM Permissions, Office of Publishing Operations, American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005.

Manufactured in the United States of America on acid-free paper.

American Psychiatric Association
1400 K Street, N.W., Washington, DC 20005
www.psych.org

The correct citation for this book is American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000.

Library of Congress Cataloging-in-Publication Data
Diagnostic and statistical manual of mental disorders : DSM-IV.—4th ed., text revision.
p. ; cm.
Prepared by the Task Force on DSM-IV and other committees and work groups of the American Psychiatric Association.
Includes index.
ISBN 0-89042-024-6 (casebound : alk. paper)—ISBN 0-89042-025-4 (pbk. : alk. paper)
1. Mental illness—Classification—Handbooks, manuals, etc. 2. Mental illness—Diagnosis—Handbooks, manuals, etc. I. Title: DSM-IV. II. American Psychiatric Association. III. American Psychiatric Association. Task Force on DSM-IV.
[DNLM: 1. Mental Disorders—classification. 2. Mental Disorders—diagnosis.
WM 15 D536 2000]
RC455.2.C4 D536 2000
616.89'075—dc21

00-024852

British Library Cataloguing in Publication Data
A CIP record is available from the British Library.

Text Design—Anne Barnes
Manufacturing—R. R. Donnelley & Sons Company

nestic Disorder, Substance-Induced Psychotic Disorder, Substance-Induced Moo Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfun tion, and Substance-Induced Sleep Disorder). The section begins with the text and cr teria sets for Substance Dependence, Abuse, Intoxication, and Withdrawal that ar applicable across classes of substances. This is followed by general comments co cerning associated features; culture, age, and gender features; course; impairmen and complications; familial pattern; differential diagnosis; and recording procedur that apply to all substance classes. The remainder of the section is organized by cl of substance and describes the specific aspects of Dependence, Abuse, Intoxicatio and Withdrawal for each of the 11 classes of substances. It should be noted that th Prevalence sections of the substance-specific texts contain survey data indicatin rates of substance use in various age groups, as well as the lifetime and 1-year pre alence of Dependence and Abuse. To facilitate differential diagnosis, the text and cr teria for the remaining Substance-Induced Disorders are included in the sections the manual with disorders with which they share phenomenology (e.g., Substanc Induced Mood Disorder is included in the "Mood Disorders" section). The diagno associated with each specific group of substances are shown in Table 1.

Substance Use Disorders

Substance Dependence

Features

The essential feature of Substance Dependence is a cluster of cognitive, behavio and physiological symptoms indicating that the individual continues use of the su stance despite significant substance-related problems. There is a pattern of repea self-administration that can result in tolerance, withdrawal, and compulsive dru taking behavior. A diagnosis of Substance Dependence can be applied to every cl of substances except caffeine. The symptoms of Dependence are similar across various categories of substances, but for certain classes some symptoms are less lient, and in a few instances not all symptoms apply (e.g., withdrawal symptoms not specified for Hallucinogen Dependence). Although not specifically listed as a terion item, "craving" (a strong subjective drive to use the substance) is likely to experienced by most (if not all) individuals with Substance Dependence. Dependen is defined as a cluster of three or more of the symptoms listed below occurring at time in the same 12-month period.

Tolerance (Criterion 1) is the need for greatly increased amounts of the substa to achieve intoxication (or the desired effect) or a markedly diminished effect w continued use of the same amount of the substance. The degree to which tolera develops varies greatly across substances. Furthermore, for a specific drug, va degrees of tolerance may develop for its different central nervous system effects. example, for opioids, tolerance to respiratory depression and tolerance to analg develop at different rates. Individuals with heavy use of opioids and stimulants

	Dependence	Abuse	Intoxication	Withdrawal	Intoxication Delirium	Withdrawal Delirium	Dementia	Amnestic Disorder	Psychotic Disorders	Mood Disorders	Anxiety Disorders	Sexual Dysfunctions	Sleep Disorders
Alcohol	X	X	X	X	I	W	P	P	I/W	I/W	I/W	I	I/W
Amphetamines	X	X	X	X	I				I	I/W	I	I	I/W
Caffeine			X										
Cannabis	X	X	X		I				I		I		I
Cocaine	X	X	X	X	I				I	I/W	I/W	I	I/W
Hallucinogens	X	X	X		I				I*	I	I		
Inhalants	X	X	X		I		P		I	I	I		
Nicotine	X			X									
Opioids	X	X	X	X	I				I	I		I	I/W
Phencyclidine	X	X	X		I				I	I	I		
Sedatives, hypnotics, or anxiolytics	X	X	X	X	I	W	P	P	I/W	I/W	W	I	I/W
Polysubstance	X												
Other	X	X	X	X	I	W	P	P	I/W	I/W	I/W	I	I/W

*Also Hallucinogen Persisting Perception Disorder (Flashbacks).

Note. X, I, W, I/W, or P indicates that the category is recognized in DSM-IV. In addition, *I* indicates that the specifier With Onset During Intoxication may be noted for the category (except for Intoxication Delirium); *W* indicates that the specifier With Onset During Withdrawal may be noted for the category (except for Withdrawal Delirium); and *I/W* indicates that either With Onset During Intoxication or With Onset During Withdrawal may be noted for the category. *P* indicates that the disorder is Persisting.

develop substantial (e.g., 10-fold) levels of tolerance, often to a dosage that would be lethal to a nonuser. Alcohol tolerance can also be pronounced, but is usually less extreme than for amphetamine. Many individuals who smoke cigarettes consume more than 20 cigarettes a day, an amount that would have produced symptoms of toxicity when they first started smoking. Individuals with heavy use of cannabis or phencyclidine (PCP) are generally not aware of having developed tolerance (although it has been demonstrated in animal studies and in some individuals). Tolerance may be difficult to determine by history alone when the substance used is illegal and perhaps mixed with various diluents or with other substances. In such situations, laboratory tests may be helpful (e.g., high blood levels of the substance coupled with little evidence of intoxication suggest that tolerance is likely). Tolerance must also be distinguished from individual variability in the initial sensitivity to the effects of particular substances. For example, some first-time drinkers show very little evidence of intoxication with three or four drinks, whereas others of similar weight and drinking histories have slurred speech and incoordination.

Withdrawal (Criterion 2a) is a maladaptive behavioral change, with physiological and cognitive concomitants, that occurs when blood or tissue concentrations of a substance decline in an individual who had maintained prolonged heavy use of the substance. After developing unpleasant withdrawal symptoms, the person is likely to take the substance to relieve or to avoid those symptoms (Criterion 2b), typically using the substance throughout the day beginning soon after awakening. Withdrawal symptoms, which are generally the opposite of the acute effects of the substance, vary greatly across the classes of substances, and separate criteria sets for Withdrawal are provided for most of the classes. Marked and generally easily measured physiological signs of withdrawal are common with alcohol, opioids, and sedatives, hypnotics, and anxiolytics. Withdrawal signs and symptoms are often present, but may be less apparent, with stimulants such as amphetamines and cocaine, as well as with nicotine and cannabis. No significant withdrawal is seen even after repeated use of hallucinogens. Withdrawal from phencyclidine and related substances has not yet been described in humans (although it has been demonstrated in animals). Neither tolerance nor withdrawal is necessary or sufficient for a diagnosis of Substance Dependence. However, for most classes of substances, a past history of tolerance or withdrawal is associated with a more severe clinical course (i.e., an earlier onset of Dependence, higher levels of substance intake, and a greater number of substance-related problems). Some individuals (e.g., those with Cannabis Dependence) show a pattern of compulsive use without obvious signs of tolerance or withdrawal. Conversely, some general medical and postsurgical patients without Opioid Dependence may develop a tolerance to prescribed opioids and experience withdrawal symptoms without showing any signs of compulsive use. The specifiers With Physiological Dependence and Without Physiological Dependence are provided to indicate the presence or absence of tolerance or withdrawal.

The following items describe the pattern of compulsive substance use that is characteristic of Dependence. The individual may take the substance in larger amounts or over a longer period than was originally intended (e.g., continuing to drink until severely intoxicated despite having set a limit of only one drink) (Criterion 3). The individual may express a persistent desire to cut down or regulate substance use. Often there have been many unsuccessful efforts to decrease or discontinue use (Criterion 4).

individual may spend a great deal of time obtaining the substance, using the sub-ce, or recovering from its effects (Criterion 5). In some instances of Substance De-dence, virtually all of the person's daily activities revolve around the substance. portant social, occupational, or recreational activities may be given up or reduced use of substance use (Criterion 6). The individual may withdraw from family ac-ties and hobbies in order to use the substance in private or to spend more time substance-using friends. Despite recognizing the contributing role of the sub-ce to a psychological or physical problem (e.g., severe depressive symptoms or mage to organ systems), the person continues to use the substance (Criterion 7). key issue in evaluating this criterion is not the existence of the problem, but rath-e individual's failure to abstain from using the substance despite having evi-ce of the difficulty it is causing.

cifiers

rance and withdrawal may be associated with a higher risk for immediate gener-edical problems and a higher relapse rate. Specifiers are provided to note their ence or absence:

With Physiological Dependence. This specifier should be used when Substance Dependence is accompanied by evidence of tolerance (Criterion 1) or withdrawal (Criterion 2).

Without Physiological Dependence. This specifier should be used when there is no evidence of tolerance (Criterion 1) or withdrawal (Criterion 2). In these individuals, Substance Dependence is characterized by a pattern of compulsive use (at least three items from Criteria 3–7).

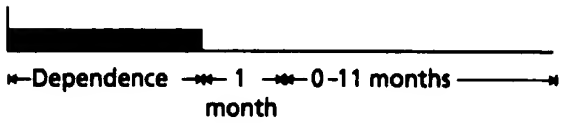
urse Specifiers

ourse specifiers are available for Substance Dependence. The four Remission ifiers can be applied only after none of the criteria for Substance Dependence or tance Abuse have been present for at least 1 month. For those criteria that require rrent problems, a remission specifier can apply only if no aspect of the criterion been present (e.g., one incident of driving while intoxicated would suffice to dis-ify the individual from being considered in remission). The definition of these types of Remission is based on the interval of time that has elapsed since the ces-n of Dependence (Early versus Sustained Remission) and whether there is con-ed presence of one or more of the items included in the criteria sets for endence or Abuse (Partial versus Full Remission). Because the first 12 months fol-ng Dependence is a time of particularly high risk for relapse, this period is des-ted Early Remission. After 12 months of Early Remission have passed without se to Dependence, the person enters into Sustained Remission. For both Early ission and Sustained Remission, a further designation of Full is given if no crite-r Dependence or Abuse have been met during the period of remission; a desig-n of Partial is given if at least one of the criteria for Dependence or Abuse has met, intermittently or continuously, during the period of remission. The differ-ation of Sustained Full Remission from recovered (no current Substance Use Dis-

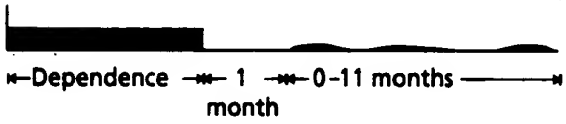
order) requires consideration of the length of time since the last period of disturbance, the total duration of the disturbance, and the need for continued evaluation. If, after a period of remission or recovery, the individual again becomes dependent, the application of the Early Remission specifier requires that there again be at least 1 month in which no criteria for Dependence or Abuse are met. Two additional specifiers have been provided: On Agonist Therapy and In a Controlled Environment. For an individual to qualify for Early Remission after cessation of agonist therapy or release from a controlled environment, there must be a 1-month period in which none of the criteria for Dependence or Abuse are met.

The following Remission specifiers can be applied only after no criteria for Dependence or Abuse have been met for at least 1 month. Note that these specifiers do not apply if the individual is on agonist therapy or in a controlled environment (see below).

Early Full Remission. This specifier is used if, for at least 1 month, but for less than 12 months, no criteria for Dependence or Abuse have been met.



Early Partial Remission. This specifier is used if, for at least 1 month, but less than 12 months, one or more criteria for Dependence or Abuse have been met (but the full criteria for Dependence have not been met).



Sustained Full Remission. This specifier is used if none of the criteria for Dependence or Abuse have been met at any time during a period of 12 months or longer.

Sustained Partial Remission. This specifier is used if full criteria for Dependence have not been met for a period of 12 months or longer; however, one or more criteria for Dependence or Abuse have been met.

The following specifiers apply if the individual is on agonist therapy or in a controlled environment:

On Agonist Therapy. This specifier is used if the individual is on a prescribed agonist medication such as methadone and no criteria for Dependence or Abuse have been met for that class of medication for at least the past month (except tolerance to, or withdrawal from, the agonist). This category also applies to those being treated for Dependence using a partial agonist or an agonist/antagonist.

In a Controlled Environment. This specifier is used if the individual is in an environment where access to alcohol and controlled substances is restricted, and no criteria for Dependence or Abuse have been met for at least the past month. Examples of these environments are closely supervised and substance-free jails, therapeutic communities, or locked hospital units.

Criteria for Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) tolerance, as defined by either of the following:
   (a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   (b) markedly diminished effect with continued use of the same amount of the substance

(2) withdrawal, as manifested by either of the following:
   (a) the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for Withdrawal from the specific substances)
   (b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

(3) the substance is often taken in larger amounts or over a longer period than was intended

(4) there is a persistent desire or unsuccessful efforts to cut down or control substance use

(5) a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects

(6) important social, occupational, or recreational activities are given up or reduced because of substance use

(7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made w rse by alcohol consumption)

Criteria for Substance Dependence *(continued)*

Specify if:

With Physiological Dependence: evidence of tolerance or withdrawal (i.e., either Item 1 or 2 is present)
Without Physiological Dependence: no evidence of tolerance or withdrawal (i.e., neither Item 1 nor 2 is present)

Course specifiers (see text for definitions):

Early Full Remission
Early Partial Remission
Sustained Full Remission
Sustained Partial Remission
On Agonist Therapy
In a Controlled Environment

Substance Abuse

Features

The essential feature of Substance Abuse is a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances. In order for an Abuse criterion to be met, the substance-related problem must have occurred repeatedly during the same 12-month period or been persistent. There may be repeated failure to fulfill major role obligations, repeated use in situations in which it is physically hazardous, multiple legal problems, and recurrent social and interpersonal problems (Criterion A). Unlike the criteria for Substance Dependence, the criteria for Substance Abuse do not include tolerance, withdrawal, or a pattern of compulsive use and instead include only the harmful consequences of repeated use. A diagnosis of Substance Abuse is preempted by the diagnosis of Substance Dependence if the individual's pattern of substance use has ever met the criteria for Dependence for that class of substances (Criterion B). Although a diagnosis of Substance Abuse is more likely in individuals who have only recently started taking the substance, some individuals continue to have substance-related adverse social consequences over a long period of time without developing evidence of Substance Dependence. The category of Substance Abuse does not apply to caffeine and nicotine. The term *abuse* should be applied only to a pattern of substance use that meets the criteria for this disorder; the term should not be used as a synonym for "use," "misuse," or "hazardous use."

The individual may repeatedly demonstrate intoxication or other substance-related symptoms when expected to fulfill major role obligations at work, school, or home (Criterion A1). There may be repeated absences or poor work performance related to recurrent hangovers. A student might have substance-related absences, suspensions, or expulsions from school. While intoxicated, the individual may neglect children or household duties. The person may repeatedly be intoxicated in situations that are

Hon. Commissioner of
Patents and Trademarks

S/N: 09/910,442

Atty: SJS/lp
Case No. 02-090-B

Re: Applicant - Bakthavatchalam, et al.

"Capsaicin Receptor Ligands"

Sir:

Please place the Patent Office receipt stamp hereon and mail to acknowledge receipt of:

(1) Transmittal Letter in Duplicate;
(2) Response to Office Action Mailed March 4, 2003;
(3) Request for Extension of Time;
(4) Information Disclosure Statement Under 37 C.F.R. §1.97(b);
(5) PTO Form 1449; and
(6) 36 Cited References.

Fee Enclosed: $290.00

Date Mailed: July 2, 2003

Respectfully,
McDonnell Boehnen Hulbert & Berghoff
Attorney for Applicant

EXHIBIT "A"

RECEIVED
OCT 17 2003
TECH CENTER 1600/2900

Hon. Commissioner of
Patents and Trademarks

S/N: 09/910,442

Atty: SJS/lp
Case No. 02-090-B

Re: Applicant - Bakthavatchalam, et al.

"Capsaicin Receptor Ligands"

Sir:

Please place the Patent Office receipt stamp hereon and mail to acknowledge receipt of:

(1) Transmittal Letter in Duplicate;
(2) Response to Office Action Mailed March 4, 2003;
(3) Request for Extension of Time;
(4) Information Disclosure Statement ~~Under~~ 37 C.F.R. §1.97(b);
(5) PTO Form 1449; and
(6) 36 Cited References.

OIPE JC41
JUL 07 2003
PATENT & TRADEMARK OFFICE

Fee Enclosed: $290.00

Date Mailed: July 2, 2003

Respectfully,
McDonnell Boehnen Hulbert & Berghoff
Attorney for Applicant

EXHIBIT "B"